Amendments to the Drawings:

The attached sheet of drawings includes an addition of the Sequence ID. Number. No new matter has been added by this Amendment. This sheet, which includes Fig. 1A, replaces the original sheet.

Attachment: Replacement Sheet

REMARKS

Prior to further examination, Applicants would request entry of the amendments set forth herein. Claim 19 has been amended, and claims 1 to 18, 20 to 77 have been cancelled. No new subject matter has been added with these amendments.

Summary of Office Action

The Examiner rejected Applicants' traverse of the Restriction Requirement and chose to examine only claims 19, 20, 33 to 35, 44, and 60. Although Applicants respectfully disagree with the Examiner's fundamental position and specifically with the rejection of the new claims, to further prosecution Applicants have cancelled all non-examined claims.

Sequence Compliance

Applicants submit herewith amendments to address the current noncompliance of the application under CFR 1.821 to 1.825, thereby obviating these objections.

Claim Objections

The Examiner objected to claims 19, 20, 33, 34, 44, and 60 for using the acronym "SUMO" and for the omission of the article "a" before the term "deSUMOylation enhancer." Applicants have amended these claims to rectify these errors, thereby obviating these objections.

Enablement Rejections

The Examiner rejected the claims under 35 U.S.C. §112, first paragraph as lacking an enabling disclosure on the following grounds:

- That there is insufficient disclosure to enable one to identify a "patient at risk" as set forth in the original claims;

- That there is insufficient disclosure to enable one to treat all forms of polyglutamine-expansion-related and protein-aggregation neurodegeneration;
- That there is insufficient disclosure to enable one to use all possible deSUMOylation enhancers to treat neurodegeneration; and
- That the fly model used to determine the efficacy of SUMO isopeptidase to treat Huntington's disease is insufficient to enable one to treat Huntington's disease in humans with SUMO isopeptidase.

In light of these rejections, Applicants have amended the application to restrict the claimed subject matter to the treatment of Huntington's disease, in patients diagnosed with Huntington's disease using a SUMO isopeptidase. Applicants submit that these amendments obviate the first three enablement rejections listed above. Specifically, Applicants have removed the language of "identifying a patient at risk", and now require that the patient already be diagnosed with the disorder. Applicants have also amended the claims to require that the disorder be Huntington's disease, which the Examiner correctly points out was the specific focus of the research disclosed in the current application. Finally, Applicants have restricted the claims to recited only SUMO isopeptidase deSUMOylation enhancers, the very substances that were the subject of the studies disclosed in the current application.

Applicants now address the Examiner's final point of rejection, namely that the *Drosophila* model for Huntington's disease used herein was insufficient to enable one of ordinary skill in the art to develop a treatment regime for Huntington's disease in humans, even using the specific SUMO isopeptidases described in the instant application. More specifically, the Examiner cites to a Wang et al. reference as teaching that fly models are insufficient, and that "proof of efficacy in mammalian models is considered a prerequisite before considering possible testing in humans." (Wang et al., page 1297, col. 2, para. 2.) The Examiner asserts from this generic statement that the use of the specific *Drosophila* model used in the instant application would not be considered sufficient by one of ordinary skill in the art to enable the development of a

treatment regime for Huntington's disease in humans. Applicants respectfully traverse this rejection.

The Examiner's principal contention is that one of skill in the art would not have considered the data from the *Drosophila* model used by Applicants sufficient to enable the treatment of humans. This is simply not supported either by the Wang et al. publication or other contemporary publications. For example, although Wang et al. do generally state that mammal models are "in theory the most faithful genetic models of the human HD condition, they also repeatedly discuss the general efficacy of fly models and more specifically the efficacy of these models for HD. For example, Wang et al. state:

> Thus, by every measure, flies expressing mutant human genes present with pathology that mimics the human disease in every important way. (Wang et al., page 1295, 1st column, 2nd paragraph.)

This general statement is corroborated by a number of contemporaneous references from around the time the application was filed, and later, that all discuss the efficacy of these fly models. For example, the reference to Jung and Bonini discusses both the interrelatedness of most polyglutamine diseases, a point Applicants have repeatedly attempted to emphasize during the prosecution of the instant application, as well as the specific utility of *Drosophila* models in developing drugs for treating these disorders. For example, Jung and Bonini state,

> Although expansion of trinucleotide repeats accounts for over 30 human diseases, mechanisms of repeat instability remain poorly understood. We show that a Drosophila model for the CAG/polyglutamine (polyQ) disease spinocerebellar ataxia type 3 (SCA3) recapitulates key features of human CAG repeat instability, including large repeat changes and strong expansion bias. (Jung & Bonini, " CREB-Binding Protein Modulates Repeat Instability in a *Drosophila* Model for PolyQ Disease; Sciencexpress, 1997.)

Similar teachings are repeated in the art and clearly demonstrate that the generic and isolated statement from Wang et al. cannot be taken as a definitive statement of the efficacy of every *Drosophila* model for every disorder. For example, three definitive

reviews of the state of the art in modeling neurodegenerative disease have all discussed the remarkable efficacy of fly models in predicting agent activity in humans. First, Bonini et al. conclude their review of the state of fly modeling with the following five revealing bullet points:

> 1. The success of modeling of fundamental aspects of several distinct human neurodegenerative diseases in fly has been an enormous advance toward discovering new molecular and cellular pathogenic events associated with disease.
> 2. Features of neurodegenerative diseases modeled in the fly include accumulation of disease proteins in abnormal aggregates, toxicity of the proteins to induce neuronal dysfunction and loss, among other features reflective of the human diseases.
> 3. Genome-wide forward genetic analysis, candidate gene approaches, and microarray analysis using these models have revealed modifiers of neurodegenerative phenotypes, including chaperones, components of ubiquitin pathways, transcription factors, signal transduction components, components of axonal trafficking, and oxidative stress pathways.
> 4. Striking mitigation of neurodegeneration by drugs and compounds including the histone deacetylase inhibitor SAHA, stress upregulator geldanamycin, and rapamycin, which induces autophagy, indicates that fly models are providing a powerful approach for therapeutic agents that have application to human disease. (Bonini et al., Annu. Rev. Genet. 2005, pp164-165.)

Likewise, peer reviewed articles by the current authors also describe the numerous advantages and efficacy of fly models at providing predictive pathways to human treatment regimes. First, in 2004 the authors wrote:

> The search for therapeutics for human diseases can be expensive and time consuming. The dominant neurodegenerative diseases of man can be faithfully modeled in invertebrates such as Drosophila as well as in mice and other mammals. Such invertebrate models exhibit the key features of these diseases such as slowly progressing degeneration, late onset, and formation of abnormal protein aggregates and, for the polyQ diseases, dependence on polyQ length. The ability to manipulate such engineered organisms allows pathogenic mechanisms to be identified and potential pharmacologic regimens to be rapidly tested. The ability to manipulate animals genetically also allows for target validation of pharmacologic agents. The excellent agreement to date of pharmacologic treatments that are effective in suppressing pathology in both flies and in

> mice gives growing confidence that invertebrate model organisms can productively speed the identification of agents that are likely to be effective at treating diseases in mammals. (Thompson et al., Bioessays 2004, pg. 494.)

Again in 2005, Thompson & Marsh write:

> Flies, on the other hand, allow excellent genetic manipulation and in vivo readouts of pathology, and the pathways are considered generally highly conserved with vertebrates, with approximately 75% of human genes known to be associated with disease having a Drosophila ortholog (Reiter et al., 2001). Drosophila is emerging as a model animal with broad applications for rapidly addressing mechanistic questions and testing therapeutic options because flies can be engineered to exhibit many of the symptoms of human disease. As would be expected from mammalian studies, for instance, decreased glutamate buffering in Drosophila is neurotoxic and provides a genetic system for analysis of glutamate-mediated neurodegeneration (Rival et al., 2004). For instance, flies recapitulate characteristic aspects of neurodegenerative diseases such as the polyglutamine- repeat diseases. Fundamental characteristics reflected in the fly include polyglutamine length-dependent pathology that is of later onset (late in larval or pupal stages), is progressive, causes motor abnormalities, and causes early death (Marsh and Thompson, 2004). (Thompson et al., Neuron 2006, pg. 170.)

They conclude their discussion with the following statement, which is particularly relevant to the Examiner's argument:

> The range and diversity of studies highlighted here represent only a fraction of the emerging studies that use Drosophila to investigate fundamental cellular mechanisms that impact human pathology, from neurodegeneration to cardiac rhythm to many other disease states. These studies demonstrate that the similarities between fundamental cellular mechanisms that affect pathology in the fly and mammalian systems are becoming more apparent with every passing year. The low cost, rapid generation time, and large repertoire of genetic and developmental tools available with Drosophila allow fly studies to speed the progress of identifying promising therapeutic strategies for testing in mammals. (Thompson et al., Neuron 2006, pg. 175.)

Of more particular interest to the current discussion is an article published in 2005 by Marsh et al., which specifically discusses the efficacy of the fly model in the study of Huntington's disease. This article states in relevant part:

> *Drosophila* transgenic models of neurodegenerative diseases such as HD have proven to be excellent models of these largely dominant human diseases by replicating most of the features of the disease, such as late onset, reduced longevity, neurodegeneration, and impaired motor function (5, 11, 12). Here, we show that expression of mutant human Htt causes widespread degeneration in the *Drosophila* CNS that correlates with degeneration of photoreceptor neurons. We then use photoreceptor neuron degeneration as a sensitive measure of the effects that drugs or genetic manipulations have on pathology, and we use this to explore combinatorial strategies of drug administration to determine whether targeting distinct cellular mechanisms can produce additive or synergistic suppression of pathology. As studies in flies have translated well to mammalian systems (5), these observations identify at least two pharmacologic combinations that are excellent candidates for testing in mammalian systems.
>
> . . .
>
> We have explored whether *Drosophila* may provide a cost-effective platform for testing large matrices of drug combinations for optimal combinations of therapeutic drugs, and to test for undesirable interactions, before proceeding to mouse models or patients suffering from HD. For this strategy to be effective, there must be good agreement between pharmacologic responses in flies and mammals. To date, the concordance of therapeutic strategies that behave similarly in flies and mammals has been excellent both in terms of pharmacologic responses in the two systems as well as for different disease models in the two systems (5), and the list continues to grow. Preclinical *in vivo* testing strategies such as those described here could result in a great savings of cost and time in developing potential disease treatments and can serve to identify treatment regimens that are very likely to provide therapeutic benefit to patients. (Marsh et al., PNAS 2006, pg 1.)

Moreover, the successful use of fly models to study neurodegenerative disease has not been limited to Huntington's disease. Specifically, a number of studies on a wide-variety of neurodegenerative disease have consistently shown the efficacy of

these models. A few examples are provided below, and the cited references are submitted with this response for the Examiner's consideration:

- **HDAC inhibitors**: A transgenic fly for HD was used to show both pharmacologically and genetically that reduction of HDACs was a possible therapeutic approach to treat HD (Steffan et al, Nature, 2001). This was followed up in a mouse study (Hockly et al, PNAS 2003) that showed that the same HDACi (SAHA) was protective in a mammalian transgenic model. Since that time, there have been multiple mouse trials for SBMA (Kennedy's disease), other HD mouse models and ALS. (Minamiyama, 2004, Ferrante, 2003)
- **Lorenzo's Oil**: Lorenzo's oil [glyceroltrioleate (C(18:1))/glyceroltrierucate (C(22:1))is used in humans for treatment of adrenoleukodystrophy (X-ALD), which is an inherited disorder of peroxisomal beta –oxidation and causes neurodegeneration, was shown to be protective in a fly model of ALD ("bubblegum mutation"), again highlighting the translation between flies and mammals. (Min et al, Science, 1999)
- **L-Dopa and dopamine agonists**: L-Dopa is used in treatment of human Parkinson's disease and this study found that L-Dopa and other dopamine agonists were protective in a fly PD model that overexpresses alpha-synuclein. (Pendleton et al, J Pharm Expt Therapeutics, 2001)
- **Cystamine**: This is an inhibitor of transglutaminase and also upregulates molecules that decrease production of reactive oxygen species. It was first identified on the basis of its ability to alter aggregation in mammalian cell culture models and was shown by us to be protective in HD flies (Apostol et al, PNAS, 2003). It was then tested in several mouse models of HD and shown to be protective as well (Dedeoglu et al, J. Neurosci, 2002; Fox et al, J. Neurochem, 2004; Karpuj, et al, Nature Med, 2002). Analogs of cystamine are currently in development for treatment of HD.
- **Congo Red**: Congo Red was shown in multiple cell culture models (Heiser et al, PNAS, 1999; Apostol et al, PNAS, 2003) to inhibit aggregation and to suppress Htt toxicity. It was then tested in a fly model of HD and was protective. (Apostol et al, PNAS, 2003) These results then translated to protection in a mouse model of HD. (Sanchez, Nature 2003)
- **Geldanamycin:** Geldanamycin reduces alpha-synuclein toxicity in mammalian cell culture and is neuroprotective in a fly model of Parkinson's disease and in a mouse MPTP model of Parkinson's disease. (Auluck, JBC, 2005; Shen, JBC, 2005)

While Applicants acknowledge that it is not possible to know absolutely whether something will work in a human until you test it in humans, everyone also agrees that some non-human models are needed and, as shown above, the fly has proven

extremely effective at identifying effective strategies more rapidly and at lower cost, than any other approach. Moreover, the stress placed on this single factor by the Examiner does not comport with the requirements for enablement set forth in the MPEP. Specifically, MPEP Section 2164.02 makes it explicitly clear that a human or mamallian "working example" is not even necessary, stating:

> An applicant need not have actually reduced the invention to practice prior to filing. In *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). (MPEP, §2164.02.)

In this case Applicants have submitted a number of working examples, including data on the efficacy of an isopeptidase enhancer in treating Huntington's disease in a fly model. The Examiner disputes the correlation of these results in humans because Applicants used a fly model rather than a mammalian model. Applicants believe that the Examiner improperly disregards the disclosures set forth in the application. The MPEP discusses "correlation" in Section 2164.02, where it states in relevant part:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. . . . If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).
>
> . . .

> A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). (MPEP § 2164.02.)

In short, nowhere do the courts or the MPEP require an "exact" correlation between the examples and the claimed invention as long as the particular model is "recognized as correlating." In fact, in evaluating the enablement of inventions relating to therapeutics Section 2107.03 places special emphasis on this point, stating:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). (MPEP, § 2107.03.)

In the current application, the Applicants report the results of a number of experiments on the disputed fly model that clearly show the efficacy of the claimed therapeutic. In addition, Applicants have provided corroborating data showing that the specific fly model used by Applicants, and other fly models as well, are commonly used in the neurodegenerative field to study the effectiveness of therapeutics, and have been used successfully to predict therapeutic treatments in humans for a number of disorders.

In contrast, the Examiner cites to a single reference (Wang et al), which never actually disputes the validity of these fly models, but rather states that "by every measure flies expressing mutant human genes present with pathology that mimics the

human disease in every important way." (Wang et al., page 1295, 1st column, 2nd paragraph.) Indeed, nowhere does the Examiner ever provide any prior art that specifically calls into question the validity of Applicants' fly model in predicting the efficacy of Huntington's disease treatments. Applicants would submit that provided the relevance of their own submissions the Examiner's continued dismissal of the working examples of the current application is unwarranted and improper.

Written Description Rejections

The Examiner also rejected claims 19, 33, 35, 44, and 60 under 35 U.S.C. §112, first paragraph as lacking sufficient written description on the following grounds:

- That there is insufficient disclosure to enable one to use all possible deSUMOylation enhancers to treat neurodegeneration.

As previously discussed, Applicants have amended the application to restrict the claimed subject matter to the treatment of Huntington's disease using a SUMO isopeptidase only. As the Examiner explicitly stated that the use of SUMO isopeptidase "meets the written description provision of 35 U.S.C. §112, first paragraph, Applicants submit that this amendment obviates the written description rejections listed above.

Indefiniteness Rejections

Finally, the Examiner also rejected all of the pending claims under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, the Examiner states that the claims do not have a step that clearly relates back to the preamble. Applicants submit that the amendments have clarified the subject matter of the invention. Specifically, Applicants have amended the claims to be directed to a treatment of Huntington's disease. The step for addressing the disease is to administer a "therapeutically effective amount" of a "SUMO isopeptidase" to a patient "diagnosed with Huntington's disease". Applicants respectfully submit that these amendments have clarified the language of the claim and the subject matter of the invention, thereby obviating this rejection.

Conclusion

In view of the foregoing amendment and response, it is believed that the application is in condition for further examination. If any questions remain regarding the allowability of the application, Applicant would appreciate if the Examiner would advise the undersigned by telephone.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 and 1.17 which may be required by this paper to Deposit Account No. 03-1728. Please show our docket number with any charge or credit to our Deposit Account.

Respectfully submitted,

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